REMARKS

In the amendments above, Claims 8 and 14 have been amended to more particularly point out and distinctly claim Applicants' invention. To limit the scope of the claims and to distinguish over Znaiden et al., U.S. Patent No. 5,268,176 ("Znaiden"), the terminology "*treatment of a disease associated with the development of calcifications in a soft tissue*" has been replaced with "*a pathological calcification*" (see, PCT patent application No. PCT/IB2004/003588, page 3, lines 17-23). Applicants consider that with this replacement the claimed invention has been limited to a single concept, "pathological calcification," which specifically means the uncontrolled formation of a calcium salt (referred to a soft tissue), as compared with broader terminology to which the Examiner objected.

Also, to make the wording more clear and specific for the Examiner, the term "on the damaged zone" has been replaced with "where the calcification is generated" to clearly show that the damage zone refers to the area in a soft tissue where a calcification has occurred. See, PCT patent application No. PCT/IB2004/003588, page 5, lines 15-20.

Further, Claims 8 and 14 have been amended to indicate the compound or a pharmaceutically acceptable salt thereof. See, for example, PCT patent application No. PCT/IB2004/003588, page 4, lines 8-13.

IDS Submission

The Examiner suggested that the copies of references submitted with and discussed in the prior Amendment should be the subject of an Information Disclosure Statement. While Applicants do not agree with the Examiner in this regard, an Information Disclosure Statement is attached hereto.

Claim Situation

As was discussed briefly with the Examiner in a recent telephone conversation, the instant application is a U.S. National Phase filing of the aforementioned PCT patent application. It is understood that during prosecution of the PCT patent application, original Claims 1-13 were replaced by new/amended Claims 1-7. At the National Phase filing Applicants submitted a copy of the PCT publication with original Claims 1-13 as well as a separate page labelled "AMENDED" and containing Claims 1-7. It is understood that Claims 1-7 were the proper claims to be examined and that they were so examined in the previous Office Action. It is respectfully submitted that the Claims 8-19 that were newly added in the previous Amendment were properly designated as "new" claims and that the Examiner's request for a Supplemental Amendment is inappropriate.

35 U.S.C. §112, First and Second Paragraph Rejections

Claims 8-19 have been rejected under the first paragraph of 35 U.S.C. 112 for lack of enablement and under the second paragraph as being indefinite.

More particularly, the claims have been rejected under § 112, first paragraph, because the specification, while enabling for methods of preparing and methods of use of myo-inositol compositions for treating certain diseases associated with the development of heterogenous nucleants which induce the development of pathological calcification in a soft tissue, does not reasonably provide enablement for preventing said diseases and/or treating any and all diseases associated with the development of heterogenous nucleants which induce the development of pathological calcification in a soft tissue. The Examiner stated that to be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

The Examiner maintained that the invention in general relates to a use of myo-inositol compositions for topical administration for treating diseases associated with the

development of heterogeneous nucleants which induce the development of pathological calcification in a soft tissue. The Examiner maintains that Grases et al. (Grases et al., "Effect of Crystallization Inhibitors on Vascular Calcifications induced by Vitamin D: A Pilot study in Sprague-Dawley rats. Cir. J. 2007:71:11-52-1156) ("Grases") teaches that pathological calcification in soft tissues (i.e., ectopic calcification) can have severe consequences when it occurs in vital organs such as the vascular or renal systems. The Examiner further maintained that Grases teaches, generally, that the development of tissue calcification requires a pre-existing injury as an inducer, whereas further progression requires the presence of other promoter factors (such as hypercalcemia and/or hyperphosphatemia) and/or a deficiency in calcification repressor factors. The Examiner maintained that Grases teaches that pyrophosphate, biphosphonates and phytate have been shown to inhibit crystallization in the form of vascular calcification and that Grases also teaches that based on the fact that phytates were found to act as vascular calcification inhibitors, the action of polyphosphates could be important in protecting against vascular calcification.

The Examiner further maintained that the claims are broad in scope. The Examiner stated that the disclosure does not provide any definition of the term "heterogenous nucleants," or does not disclose the connection between the administration of myo-inositol hexaphosphate and its effect on heterogenous nucleants, or how the effect on heterogenous nucleants relates to the contemplated effects to be achieved in practicing the instant invention. The Examiner further noted that prior Claim 1 recites the term "pathological calcification in a soft tissue," which encompasses pathological calcification in soft tissues of any and all mammalian species. The Examiner maintained that because the therapeutic response to be achieved would reasonably vary depending upon the specific mammalian species, targeted soft tissue, location of the soft tissue, and the pharmacodynamic/pharmacokinetic profile of myoinositol hexaphosphate, the level of predictability in practicing the claimed invention would be greatly diminished.

The Examiner further noted that the specification discloses a study involving the topical administration of phytate to rats. The Examiner maintains that based on the instant disclosure, Applicants have provided specific direction or guidance only for a general method of using a myo-inositol composition. The Examiner stated that extrapolation of the exemplified rat data disclosed by Applicants to any and all mammalian species would reasonably require extensive experimentation in order to achieve the contemplated treatment effects in practicing the instant claimed invention commensurate with the claims.

The Examiner further maintained that in view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

Claims 8-19 have been rejected under § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner maintains that the claims herein provide for the use of a composition including myo-inositol hexaphosphate in a form adapted to topical administration for the manufacture of a formulation for the prevention and/or treatment of a disease associated with the development of heterogenous nucleants which induce the development of pathological calcification in a soft tissue.

The bases of the rejections under the first and second paragraphs of § 112 are interrelated and somewhat overlapping, and Applicants do not necessarily agree with the Examiner's positions. However, the Examiner's attention is directed to the amendments above wherein Claims 8 and 14 have specifically been amended in such a way to clarify that the subject matter claimed is both enabling and definite. Therefore, the rejections based upon the first and second paragraphs of § 112 should be withdrawn.

35 U.S.C. §§ 102(b) and 103(a) Rejections

Claims 8-19 have been rejected under 35 U.S.C.§102 (b) or 103(a) as being unpatentable over Znaiden. Applicants respectfully traverse these rejections.

The Examiner maintains that Znaiden anticipates the present invention since they teach topical compositions containing inositol hexaphosphate for use in spider veins, features which the Examiner considers to be included in the claims (same active compound, same route of administration, same target (soft tissue)). The treatment effect and kind of calcifications (dependent claims) are considered to be inherent features. Also, as a response to the arguments filed, the Examiner considers that phytate used for treating spider veins ultimately reach the blood stream.

In addition to the arguments set forth in the previous Amendment (where it is indicated that the target is not the soft tissue itself but it is the calcification), which arguments are incorporated herein by reference, it should be appreciated that Applicants do not agree with the Examiner's statements, specially when indicating that phytate can "ultimately reach the blood stream." In particular, at Col. 3, lines 7-11 and 18-24, it is stated:

> "The hydroxyl groups may allow the molecule to readily penetrate **the most superficial layers of skin** which are slightly polar because they lack a significant phopholipid concentration." and "Once a highly polar molecule reaches viable tissue, **it will be repulsed by cell membrane phospholipids and remain in the intercellular space**. Instead of being lost through dissipation, **the molecules remain sequestered and form a stable depot**, which creates a high osmotic gradient necessary for the collapse of an offending vessel." (Emphasis added.)

According to the different passages it is clear that the active molecule after crossing the most superficial layers remains in the intercellular space, and nothing leads to the conclusion that the molecule can reach the blood stream. In fact, when the different layers of skin are analyzed, it is of general knowledge that these are (in order from outer to inner part of the skin):

- Stratum corneum: the outermost layer of the epidermis and is formed of surface epithelial cells.

- Keratinous layer: part of epidermis

- Regenerative layer: part of epidermis

- Stratum papillarosum: upper layer of dermis and in contact with epidermis.

- Reticular layer: deepest layer of dermis.

Blood vessels cannot be found until Stratum papilarosum. Consequently and according to the text of Zaiden, it is not obvious that the active molecule can reach this layer and enter the blood vessels. In fact, the discovery 2003 that phytate could reach the blood stream and, finally, could be eliminated through the urine was a surprising fact because it was thought that the high electric charge of this molecule (6-7 charges at physiological pH) leads to a low penetration degree, which is reduced when going to inner layers.

Znaiden suggests the formation of a deposit in the superficial layers which forms an osmotic gradient. Applicants demonstrate the absorption of the active compound (entering the blood vessels) and systemic effect.

Furthermore, the possible overlap between the targeted population of Znaiden and in the instant invention has no basis at all, since the origin of spider veins has nothing to do with the occurrence of scales of calcium salts in the body. As stated by Znaiden:

> [Spider veins are] characterized by the visual dilation of one or several superficial skin arterioles in the human body. A number of physiological circumstances may contribute to the formation of these aberrant arterioles and, in some cases, they are the symptomatic of a systemic, pathological disorder .... More particularly, dilated arterioles are readily observed based on their characteristic shape and irritated color cause by oxygenated blood flowing close to the surface of the skin. (Col. 1 lines 16-21 and 39-42)

There is no mention nor are there any suggestion in the explanation about spider veins disorder which might lead a skilled person in the art to think that pathological calcifications and spider veins disorder can be related in any way. Both are different targets and their studies are completely different. Consequently, there is no reason to consider a possible overlap of patients. It can occur in an hypothetical case that a person is suffering from both disorders but always one independently of each other.

In view of the comments above and the amendments to the claims, it is believed that it can be appreciated that the subject matter calimed herein is patentable over Znaiden. Therefore, the rejections under §§ 102(b) and 103(a) should be withdrawn.

Applicants believe that the amendments to the claims above are intended to put the claims herein in allowable condition and to not raise issues that would require furher serarching or consideration by the Examiner. Therefore, entry of this paper is respectfully requested.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

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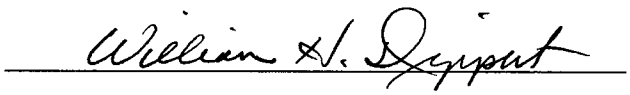

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